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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,154	04/24/2002	George N. Cox III	4152-3-PUS	6320

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,154	COX ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-124* is/are pending in the application.

4a) Of the above claim(s) *71-76,87-89,97-101,107,108,111 and 119-121* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-70,77-86,90-96,102-106,109,110,112-118 and 122-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application, Amendments, And/Or Claims

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1646, Examiner: Xiaozhen Xie.

The Declaration under 37 CFR 1.132 of Dr. George Cox submitted on 15 February 2006 is acknowledged. Applicant's amendment of the claims filed 15 February 2006 is acknowledged.

Claims 1-66 have been cancelled. New claims 67-124 have been added. Claims 67-124 are pending. Claims 71-76, 87-89, 97-101, 107, 108, 111 and 119-121 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 67-70, 77-86, 90-96, 102-106, 109, 110, 112-118 and 122-124 are under examination.

Claim Rejections Withdrawn

The rejection of claims 1, 2, 24, 26, 43 and 52 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 1, 6, 7, 24, 25, 28-31, 37 and 43 under 35 U.S.C. 102(b) as being anticipated by Sytkowski et al. (WO 99/02709), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 15, 16, 19, 20, 40 and 57 under 35 U.S.C. 102(b) as being anticipated by Sytkowski et al. (U S. Patent NO: 6,242,570), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claim 41 under 35 U.S.C. 102(b) as being anticipated by Amoresano et al. (Glycobiology, 1998, Vol. 8, pp. 779-790), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 2, 26, 42, 45, 46, 52, 53, 62-65 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), in view of Curtis et al. (U.S. Patent NO: 5,073,627), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 2-5 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), in view of Mapelli et al. (U.S. Patent NO: 5,519,115), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 22, 23, 58, 59 and 66 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (U S. Patent NO: 6,242,570), in view of Mapelli et al. (U.S. Patent NO: 5,519,115), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over Amoresano et al. (Glycobiology, 1998, Vol. 8, pp. 779-790), in view of Mapelli et al.

(U.S. Patent NO: 5,519,115), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 32 and 33 under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), in view of Strom et al. (WO 99/02711), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 38 and 44 under 35 U.S.C. 102(a) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), is withdrawn in response to Applicant's cancellation of the claims.

Claim Objections Maintained

The newly added claims 79, 103, 116 and 122 remain objected for reciting non-elected species.

Claim Rejections Maintained/New Grounds of Rejections

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The newly added claims 70 and 96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 70 and 96 now recite "an EC_{50} of less than about 1000 ng/ml in an EPO-dependent in vitro bioassay using a cell line that proliferates in response to EPO". The claims are indefinite because the EC_{50} varies depending on what assay system is used.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The newly added claims 67-70 and 77-84 are rejected under 35 U.S.C. 102(a) as being anticipated by Sytkowski et al. (WO 99/02709) for reasons of record in the previous office action (15 August 2005).

Applicant argues that the claims are directed to direct fusions between the recited proteins and an Ig domain, i.e., fusions without an intervening peptide linker. Applicant refers the Examiner to the Declaration under 37 CFR 1.132 of Dr. George Cox, which discusses that although Sytkowski et al. postulate a direct fusion between EPO and IgG-Fc, the publication is non-enabling for this fusion because the amino acids at the end of EPO and the beginning of mouse or human IgG-Fc domains are such that they cannot be joined by a Bam HI site or any other restriction enzyme site without using a peptide linker or changing the amino acid sequences of the protein. Therefore, WO 99/02709 does not actually teach an EPO-IgG fusion protein as claimed in claim 67 (formally claim 1) because the publication is non-enabling.

Applicant's arguments have been fully considered but have not been found to be persuasive.

Claim 67 (formally claim 1) is directed to a fusion protein comprising a soluble protein joined without an intervening peptide linker to an Ig domain that does not contain a variable region, wherein the soluble protein is selected from the group consisting of a growth factor, a cytokine that is not IL-10, and an active variant thereof. As stated in the previous office action, WO 99/02709 teaches fusion proteins comprising erythropoietin or erythropoietin-like molecules and Ig polypeptide chains. There is no limitation for the amino acid sequence of the fusion proteins, e.g., SEQ ID for erythropoietin or Ig polypeptide chains. On page 6, lines 12-17, WO 99/02709 describes that the term "erythropoietin" also encompasses biologically active fragments of erythropoietin, erythropoietin mutants and erythropoietin analogs, variants and derivatives, referred to as erythropoietin-like molecules. Also, on page 14, lines 3-5, WO 99/02709 describes that immunoglobin and biologically active fragments, analogs, mutants, variants and derivatives thereof, are encompassed in the Invention. Indeed, the instant application also encompassing active variants of the proteins for constructing the fusions, e.g., mutants of EPO (pp. 7, lines 24-26). Therefore, it is enabled for generating a fusion protein between an erythropoietin or erythropoietin-like molecules and an Ig polypeptide chain without an intervening peptide linker.

The newly added claims 106, 109, 110, 112, 113 and 116, are rejected under 35 U.S.C. 102(e) as being anticipated by Sytkowski et al. (U. S. Patent NO: 6,242,570 which has a filing date on 10 July 1997) for reasons of record in the previous office action (15 August 2005).

Applicant argues that with regard to claims 106, 109 and 110, which recite a homomultimeric protein joined without an intervening peptide linker, Sytkowski et al., as in the WO 99/02709, provide absolutely no teaching or guidance whatsoever with regard to how to make a direct fusion between EPO monomers. Applicant argues that as discussed by Dr. Cox, it is not possible to create a direct fusion between EPO monomers this way because the Bam H1 site will always result in the creation of extra amino acids other than the EPO amino acids, which form a peptide linker. Applicant argues that Sytkowski et al. taught a method that was inoperable for the production of a direct fusion as taught and claimed in the present application, and therefore the '570 patent is non-enabling for the teaching of a direct fusion of EPO to other EPO proteins.

Applicant argues that with regard to claims 116, 112 and 113, which recite a homomultimeric protein joined with a peptide linker that has been limited to a linker of between 2 and 7 amino acids and consisting of only glycine or serine, the '570 patent teaches away from the use of such small linkers. Applicant argues that the only multimeric fusion protein exemplified in the '570 patent is an EPO-EPO dimer, joined by a peptide linker of 17 amino acids. Applicant argues that the '570 patent clearly teaches that the linker should be at least 10 amino acids in length, and preferably longer.

Applicant's arguments have been fully considered but have not been found to be persuasive.

With regard to claims 106, 109 and 110, the independent claim (claim 106) is directed to a homomultimeric fusion protein comprising two or more copies of a member of the Growth Hormone (GH) supergene family joined without an intervening peptide

linker. Most members of the GH family protein do not share identical amino acid end, e.g. an amino acid end encoded by a nucleotide sequence containing a Bam H1 site. The specification describes that members of the GH supergene family generally have limited amino acid or DNA sequence identity (pp. 7, lines 18-19). As stated in the previous office action, the '570 patent teaches a multimeric fusion protein comprising two or more members of erythropoietin joined with or without a peptide linker. On column 3, lines 30-33, the '570 patent describes the fusion proteins have a formula of R_1-R_2 or R_1-L-R_2, where R_1 and R_2 are substantial similar or identical protein molecules and L is a linker, typically a peptide. The '570 patent teaches that the protein molecules are erythropoietin (column 3, lines 38-40). The '570 patent further defines that fusion proteins comprising biologically active fragments, analogs, mutants, variants or derivatives of the naturally–occurring proteins (column 7, lines 12-23). Such proteins do not necessary to have a Bam H1 site at the end of the amino acid sequence. As stated above, there is no sequence limitation for the monomer molecule, e.g., SEQ ID for an erythropoietin molecule. Therefore, it is enabled for generating a homomultimer fusion protein comprising two or more copies of erythropoietin without an intervening peptide linker.

With regard to claims 116, 112 and 113, the claims are directed to a homomultimeric fusion protein comprising two or more copies of erythropoietin joined by at least one peptide linker that consists of a mixture of between 2 and 7 amino acid residues selected from the group consisting of: glycine and serine. There is no limitation on how many of such linker will be in the fusion protein, for example, in an

erythropoietin dimer, and therefore, the claims do not limit the length of a peptide linker. As stated in the previous office action, the '570 patent teaches the lengths of the linker and the amino acids suitable for the linker sequence, including glycine, asparagines and serine (column 4, lines 49-53 and lines 59-67). Therefore, the '570 patent anticipates the instant invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The newly added claims 90-96 and 102-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), in view of Mapelli et al. (U.S. Patent 5,519,115) for reasons of record in the previous office action and the following.

As stated above, WO 99/02709 teaches fusion proteins comprising erythropoietin or erythropoietin-like molecules and Ig polypeptide chains. WO 99/02709 also teaches that additional nucleotides encoding a flexible protein sequence (e.g., about 1-20 amino acids can be inserted prior to the hinge region nucleic acid sequence (pp. 17, lines 8-16). WO 99/02709, however, does not teach the peptide linkers consisting of a mixture of 2, 4 or 7 amino acid residues selected from the group consisting of glycine and serine, nor teach the linker as SerGly or SEQ IDs: 1 or 3.

The '115 patent teaches small bridges of 5 amino acids or less to link monomers. The '115 patent teaches that undesirable peptide secondary structures such as alpha helix or beta strands which may dominating the structure of the resulting oligomer and hinder potential interactions between the monomers generally require more than five amino acids in length. The '115 patent teaches that Gly side chain moieties are unlikely to sterically hinder any potential folding of the oligomer, and cannot participate in energenically stable bond structure. The '115 patent further gives several example of such Gly-rich linkers, including one identical to the SEQ ID NO: 1 of the instant application (column 24, lines 21 through column 25, lines 7).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the teachings of WO 99/02709, with those of the '115 patent to use small Gly-rich linkers such as S-G-G-S (SEQ ID NO: 1) to link erythropoietin or erythropoietin-like molecules and Ig polypeptide chains. One of ordinary skill in the art would have been motivated to combine the teachings, because WO 99/02709 teaches a fusion protein comprising erythropoietin or erythropoietin-like molecules and Ig polypeptide chains which can be linked by a flexible protein sequence about 1-20 amino acids in length, and the '115 patent teaches such linker. Therefore, the combined teachings provide a reasonable expectation of successfully linking the two polypeptide components without affecting the structure and biological activity of the resulting fusion protein.

Applicant argues that the size and amino acid sequence of peptide linker can have a profound impact on the bioactivities of fusion proteins, and it is not obvious or

correct that any linker could be used to create any fusion proteins. Applicant cited references of Robinson et al., Qiu et al., and Chang et al. to support that the length of the linker can dramatically impact the biological activity of the resulting fusion protein. Applicant further argues that the linkers of the '115 patent is in contrast to the instant invention that the '115 patent claims a fusion protein between oligopeptides that prefers to have no secondary structures, wherein the instant fusion proteins are between large proteins that contain alpha helices and beta strands. Applicant points out that the on column 25, lines 29-41, the '115 patent teaches use of longer bridges. Applicant argues that the combination of WO 99/02709, with those of the '115, would not provide further information with regard to the construction of EPO-Ig fusions than WO 99/02709 alone.

Applicant's arguments have been fully considered but have not been found to be persuasive.

First, independent claim 90 is directed to a fusion protein comprising a soluble protein and an Ig domain, wherein the soluble protein is selected from the group consisting of a growth factor, a cytokine that is not IL-10 or an interferon, and an active variant thereof. There is no limitation reciting that the fusion protein is EPO-Ig. It is generally acknowledged, as taught by the references, that the size and amino acid sequence of peptide linker can have a profound impact on the bioactivities of fusion proteins, and it is not obvious or correct that any linker could be used to create any fusion proteins. The '115 patent teaches a guidance for using linkers when making fusion proteins, and such linkers should not have secondary structures such as alpha helix or beta strands which may dominating the structure of the resulting oligomer and

hinder potential interactions between the monomers. Applicant misinterpreted the '115 patent as whether the secondary structure, e.g. alpha helices or beta strand, is present in the protein component. The '115 patent indicates undesired secondary structure in the linking sequence. As for the longer bridges discussed in column 25, lines 29-41, the '115 patent specifies the extracellular domains of transmembrane protein which are useful for transporting across cell membrane.

The newly added claims 114, 115, 117, 118, and 122-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (U. S. Patent NO: 6,242,570), in view of Mapelli et al. (U.S. Patent 5,519,115).

As stated above, the '570 patent teaches a multimeric fusion protein comprising two or more members of erythropoietin joined with or without a peptide linker. The '570 patent describes the fusion proteins have a formula of R_1-R_2 or R_1-L-R_2, where R_1 and R_2 are substantial similar or identical protein molecules and L is a linker, typically a peptide. The '570 patent teaches that the protein molecules can be erythropoietin (column 3, lines 38-40) or other cytokines, growth factors and hormones, for example, molecules listed on column 5-7. Many of these proteins are GH supergene family proteins and have similarity in terms of structure and function. The '570 patent, however, does not teach the peptide linkers consisting of a mixture of 2, 4 or 7 amino acid residues selected from the group consisting of glycine and serine, nor teach the linker as SerGly.

The '115 patent teaches small bridges of 5 amino acids or less to link monomers. The '115 patent teaches that undesirable peptide secondary structures such as alpha helix or beta strands which may dominating the structure of the resulting oligomer and hinder potential interactions between the monomers generally require more than five amino acids in length. The '115 patent teaches that Gly side chain moieties are unlikely to sterically hinder any potential folding of the oligomer, and cannot participate in energetically stable bond structure. The '115 patent further gives several example of such Gly-rich linkers, including one identical to the SEQ ID NO: 1 (S-G-G-S) of the instant application (column 24, lines 21 through column 25, lines 7).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the teachings of the '570 patent, with those of the '115 patent to use small Gly-rich linkers such as Ser-Gly to link two or more members of erythropoietin molecules or erythropoietin with other GH superfamily members. One of ordinary skill in the art would have been motivated to combine the teachings, because the '570 teaches a multimeric fusion protein comprising two or more members of erythropoietin, or other GH superfamily proteins joined with a peptide linker, and the '115 patent teaches such a linker. Therefore, the combined teachings provide a reasonable expectation of successfully linking the polypeptide components without affecting the structure and biological activity of the resulting fusion protein.

The newly added claims 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski et al. (WO 99/02709), in view of Strom et al. (WO 99/02711) for reasons set forth in the previous office action.

Applicant argues that claim 85 and 86 are directed to a method to produce the fusion protein of claim 67 (fusion protein without an intervening linker), and that since WO 99/02709 fails to provide an enabling disclosure that teaches an EPO-Ig fusion protein without an intervening linker, the deficiencies are not remedied by the teachings of Strom et al, as teaching of expression and purification steps does not provide a teaching of the claimed fusion protein.

Applicant's arguments have been fully considered but have not been found to be persuasive.

As discussed above, WO 99/02709 does provide an enabling disclosure that teaches a fusion protein encompassed in the instant invention without an intervening linker.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 105 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 105 recites "further comprising purifying dimeric fusion protein". The independent claim 90 does not contain dimeric fusion protein.

Conclusion

NO CLAIM IS ALLOWABLE.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

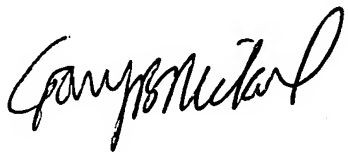
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nicole, Ph.D. can be reached on 571-272-0835. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
June 9, 2006



GARY B. NICKOL, PH.D.
PRIMARY EXAMINER